**RESVERATROL**

**A REAL BENEFIT OR JUST A CONUNDRUM?**

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**HISTORY**

Ayurvedic medicine - “darakchasava”, a well-known Indian herbal preparation of *Vitis vinifera* L. Used as cardiotonic

- 1939 from White Hellebore
- 1959 from Eucalyptus wandoo, Eucalypt tree native to Western Australia
- 1963 from Japanese Knotweed (syn. Polygonum cuspidatum)


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**RES-VERATROL**

RES: might be an abbreviation of the class of molecules: resveratrol belongs to the *res*orcins
VERATR: abbreviation of the plant name, *Veratrum*
OL: is generally used for indicating hydroxyl groups: resveratrol has three of them.

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**WHY PLANTS SYNTHESISE RESVERATROL?**

Plants, when stressed by mold, various infections, ultraviolet radiation, or injury, synthesize specialized polyphenol compounds phytoalexins.

- Resveratrol - a potent phytoalexin, acts as the plant’s antibiotic or fungicide to ward off attacks, particularly from various fungi.
- Found in Japanese Knotweed, peanut skins, grapes, and blueberries, Scots pine.

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**SIRTUIN ACTIVATOR**

- Mimicking the positive effect of calorie restriction
- Interacts with multiple molecular targets
- Promising field of the medicinal chemistry
- Improves the response to insulin
- Increase the number and activity of mitochondria in obese mice
- Resveratrol has low bioavailability
- Human trials with a formulation of resveratrol with improved bioavailability and with a synthetic SIRT1 activator are in progress
- New SIRT1 activators that are up to 1000 times more effective than resveratrol have recently been identified

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**SIRTUIN1 (SIRT1)**

- Deacetylases - member of the sirtuin family
- Dependent on NAD+ for their activity.
- Down-regulates p53 activity - increasing lifespan, cell survival, and neuroprotection.
- Deacetylates peroxisome proliferator-activated receptor-gamma and its coactivator 1a, promoting fat mobilization, increasing mitochondrial size & number, positively regulating insulin secretion.
- Link nutrient availability & energy metabolism. Activated by calorie restriction
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**VASCULAR HEALTH**

- Resveratrol restored endothelial function in type 2 diabetes by inhibiting TNF-induced activation of NAD(P)H oxidase
- Thus preserving eNOS phosphorylation
- Potential for new treatment approaches to promote vascular health in metabolic diseases.

(Arterioscler Thromb Vasc Biol. 2009;29:00-00)

**ANTICANCER EFFECT**

Interfere with all 3 stages of cancer:
- Initiation - neutralises free radicals
- Promotion - suppress inflammation
- Progression - inhibits angiogenesis

The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest; upregulation of p21Cip1/WAF1, p53, and Bax; downregulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-xL, and GAPs.


**ANTI-CANCER PROPERTIES OF RESVERATROL**

- Inhibits experimental tumorigenesis in a wide range of animal models
- Targets many components of intracellular signaling pathways including pro-inflammatory mediators, regulators of cell survival and apoptosis, tumor angiogenic and metastatic switches by modulating a distinct set of upstream kinases, transcription factors and their regulators

**INHIBITION OF GaSTRIC CANCER CELL PROLIFERATION BY RESVERATROL: ROLE OF NITRIC OXIDE**

RESULTS

Resveratrol inhibits DNA synthesis in gastric adenocarcinoma SNU-1 cells
Resveratrol stimulates NOS activity in SNU-1 cells
Resveratrol and ionomycin deplete cellular NADPH
High-resveratrol concentration induces apoptosis in SNU-1 cells.

Oksana Holian, ShaHid WaHid, Mary Jo Atten, and Bashar M. Attar
Department of Medicine, Division of Gastroenterology, Cook County Hospital and Hektoen Institute for Medical Research, Chicago, Illinois 60612
Am J Physiol Gastrointest Liver Physiol 282: G809–G816, 2002

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Increases Chemoradiation Effectiveness
Enhances the effectiveness of Taxol in lung cancer by altering multiple pathways including p21waf1, p27kip1, PTEN, E-cadherin, EGFR and Bcl-2
(Anticancer Res. 2003 Sep-Sep 23(5A): 4039-46.)
Selectively down-regulates the expression of ant apoptotic proteins Bcl-xL and myeloid cell differentiation factor-1 (Mcl-1) and up-regulates the expression of proapoptotic proteins Bax and apoptosis protease activating factor-1 (Apaf-1).
(Anticancer Res. 2004 Jan-Jun 24(1A):71-84.)
Reverses drug resistance of Taxol in prostate cancer by downregulating tyrosine kinases and STAT1.
(Anticancer Res. 2007 Nov-Dec 27(6B):3153-67.)

Suppress proliferation
induces apoptosis through
the caspase-8-dependent pathway (receptor-mediated; type I)
the caspase-9-dependent pathway (mitochondrial; type II)
p53 activation pathway: p53 is a tumor suppressor gene
Huang et al. found that resveratrol-induced apoptosis occurred only in cells expressing wild-type p53 (p53+/+), but not in p53-deficient (p53−/−) cells
suppressing NF-κB, a nuclear transcription factor that regulates the expression of various genes involved in inflammation, cytoprotection, and carcinogenesis

Several reports suggest that resveratrol suppresses proliferation of colon cancer cells:
In human wild-type p53-expressing HCT116 colon carcinoma cell line and HCT116 cells with both p53 alleles inactivated by homologous recombination.

Mahyar-Roemer et al. Study:
Resveratrol induced apoptosis independently of p53, the apoptosis was mediated primarily by mitochondria and not by a receptor pathway

Dr Andrew Weil

I believe that how we eat is an important determinant of how we feel and how we age. I also believe that food can function as medicine to influence a variety of common ailments.

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